UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/506,936	06/06/2005	Motowo Nakajima	PC/4-32388A	6976

75074 7590 03/18/2008

NOVARTIS INSTITUTES FOR BIOMEDICAL RESEARCH, INC.
400 TECHNOLOGY SQUARE
CAMBRIDGE, MA 02139

EXAMINER	
STONE, CHRISTOPHER R	
ART UNIT	PAPER NUMBER
1614	
MAIL DATE	DELIVERY MODE
03/18/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/506,936	NAKAJIMA ET AL.	
	Examiner	Art Unit	
	CHRISTOPHER R. STONE	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 7-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 7-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *09/08/2004, 11/08/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of N-hydroxy-2(R)-[[4-methoxyphenylsulfonyl](3-picolyl)-amino]-3- methylbutanamide hydrochloride in the reply filed on February 4, 2008 is acknowledged.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 3 and 4 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-5 and 7-9 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses chemicals, such as compounds of formula I, which

meet the written description and enablement provisions of 35 USC 112, first paragraph. However, claim(s) 2-5 and 7-9 are directed to encompass prodrug esters and derivatives, which only correspond in some undefined way to specifically instantly disclosed chemicals. None of these prodrug esters and derivatives meet the written description provision of 35 USC § 112, first paragraph, due to lacking chemical structural information for what they are and chemical structures are highly variant and encompass a myriad of possibilities. The specification provides insufficient written description to support the genus encompassed by the claim.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of the above specifically disclosed chemical structures, the skilled artisan cannot envision the detailed chemical structure of the encompassed prodrug esters and derivatives, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The chemical structure itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found

unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence. Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.* , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

Therefore, only the above chemically structurally defined chemicals, but not the full breadth of the claim(s) meet the written description provision of 35 USC § 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC § 112 is severable from its enablement provision. (See page 1115.)

Claims 1-5 and 7-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of pancreatic and cervical cancers/tumors, does not reasonably provide enablement for the treatment of other cancer/tumors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Claims 1-5 and 7-10 are drawn to a method of treating cancer/tumors comprising administering radiotherapy or cytotoxic therapy in combination with heat shock and further comprising the administration of N-hydroxy-2(R)-[[4-methoxyphenylsulfonyl](3-picolyl)-amino]-3- methylbutanamide hydrochloride . The prior art indicates that cancer is a group of maladies not treatable with one medicament or therapeutic regimen. No single chemotherapeutic drug is useful for the treatment of every case of cancer. In fact, some types of cancer do not respond well to any known chemotherapeutic drugs (see Oxford Textbook of Oncology, p. 451, Column 2, last paragraph). These negative results indicate a lack of predictability in the art. Furthermore the Applicant has provided no working examples demonstrating the efficacy of this treatment on cancers, other than pancreatic and cervical cancer. For these reasons, it would take undue experimentation by one of ordinary skill in the art to use this method to treat cancers, other than pancreatic and cervical, with a reasonable expectation of success.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3 and 4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3 and 4 provide for the use of a matrix metalloproteinase inhibitor, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5 and 7-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Macpherson et al (WO 96/40101), in view of Evans et al, further in view of Kouloulias et al.

Note: For the purpose of this rejection, claims 3 and 4 are being interpreted as being drawn to a method of treatment.

Claims 1-5 and 7-10 are drawn to a method of treating cancer comprising administering radiotherapy or cytotoxic therapy in combination with heat shock and further comprising the administration of N-hydroxy-2(R)-[[4-methoxyphenylsulfonyl](3-picolyl)-amino]-3- methylbutanamide hydrochloride and a package comprising N-hydroxy-2(R)-[[4-methoxyphenylsulfonyl](3-picolyl)-amino]-3- methylbutanamide hydrochloride and instructions for its use.

Macpherson et al teaches N-hydroxy-2(R)-[[4-methoxyphenylsulfonyl](3-picolyl)-amino]-3- methylbutanamide hydrochloride as a matrix metalloproteinase inhibitor, useful in the treatment of cancer (p. 16, paragraph 6 and p. 28, example 1a). Macpherson et al does not teach the use of N-hydroxy-2(R)-[[4-methoxyphenylsulfonyl](3-picolyl)-amino]-3- methylbutanamide hydrochloride in combination with radiotherapy or cytotoxic therapy and heat shock therapy to treat pancreatic cancer. Evans et al teaches that matrix metalloproteinase inhibitors are useful in the treatment of pancreatic cancer (p. 1865, abstract, especially last sentence). Kouloulias et al teaches that chemotherapy in combination with hyperthermia (heat shock) and radiotherapy is particularly advantageous for the treatment of pancreatic cancer, relative to other regimens (p. 564, abstract, Conclusions heading). Therefore it

would have been obvious to one of ordinary skill in the art at the time of the instantly claimed invention to treat pancreatic cancer by administering radiotherapy and N-hydroxy-2(R)-[[4-methoxyphenylsulfonyl](3-picolyl)-amino]-3- methylbutanamide hydrochloride in combination with heat shock therapy since this multimodality therapy was known to be useful in the treatment of pancreatic cancer and N-hydroxy-2(R)-[[4-methoxyphenylsulfonyl](3-picolyl)-amino]-3- methylbutanamide hydrochloride was known to be useful for the same purpose. Applicant is reminded of in re Kerkhoven, which affirmed that "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) In the instant case the idea of combining the treatments flows logically from their having been taught individually to be useful for the same purpose (i.e. the treatment of pancreatic cancer) in the prior art. Additionally, it would have been obvious to one of ordinary skill in the art at the time of the instantly claimed invention to package an oral (enteral) dosage form of N-hydroxy-2(R)-[[4-methoxyphenylsulfonyl](3-picolyl)-amino]-3- methylbutanamide hydrochloride with instructions for its use in the aforementioned multimodality therapy, since the prior art renders the therapy itself obvious and this packaging and oral dosage forms are common in the pharmaceutical art for distribution and accurate and convenient administration of a drug/regimen.

Claim Objections

The disclosure is objected to because of the following informalities: claim 10 contains a typographical error. It is apparent from the disclosure that the word inhibitor has been omitted and that the claim is intended to encompass "... an effective amount of a matrix metalloproteinase *inhibitor*." Therefore, the examination has been conducted as though the claim reads "...an effective amount of a matrix metalloproteinase *inhibitor*." Appropriate correction is required.

Additionally, claim 7 is directed to the method of claim one, wherein the matrix metalloproteinase inhibitor is on of the compounds disclosed in published international patent application Nos. WO 98/14424, WO 97/22587. etc.. The incorporation of essential material in the specification by reference to an unpublished U.S. application, foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference, if the material is relied upon to overcome any objection, rejection, or other requirement imposed by the Office. The amendment must be accompanied by a statement executed by the applicant, or a practitioner representing the applicant, stating that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter. 37 CFR 1.57(f).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRISTOPHER R. STONE whose telephone number is

(571)270-3494. The examiner can normally be reached on Monday-Thursday, 7:30am-4:00pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

03March2008
CRS

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614